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Bisphosphonate Therapy in Fibrous Dysplasia

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Fibrous dysplasia is proliferation of fibrous tissue within the bone marrow causing osteolytic lesions and pathologic fractures. Recently, second generation bisphosphonates have shown promise in the treatment of patients with fibrous dysplasia. In the current study, six patients with fibrous dysplasia were treated with either oral alone or oral and intravenous bisphosphonates. The participants were observed for changes in N-telopeptide, pain score, and radiographic changes. In the current study, the combination bisphosphonate therapy diminished pain, prevented fractures, lowered N-telopeptide values, and led to partial resolution of fibrous dysplasia lesions.

Fibrous dysplasia is a rare, nongender selective, noninherited, congenital disorder most commonly occurring in patients younger than 30 years of age. The hallmark of this disease is extensive proliferation of fibrous tissue within the bone marrow causing osteolytic lesions and pathologic fractures.[7] It represents approximately 2.5% of known bone disorders and comprises approximately 7% of benign bone tumors.[4] Fibrous dysplasia most commonly occurs in the long bones of the body, the ribs, and in the skull. However, any bone may become affected. The symptom complex may include bone pain, localized deformities, and repeated fragility fractures of the affected region during childhood and adolescence. Fibrous dysplasia occurring in only one location (monostotic form) is approximately six times more common than fibrous dysplasia occurring in multiple locations (polyostotic form).[5] The polyostotic form may occur in conjunction with café au lait spots and multiple endocrinopathies and is defined as the McCune-Albright syndrome.[1] This is a mosaic gene disorder with a G protein dysfunction.[15] There has been little change throughout the history of the treatment of patients with fibrous dysplasia. The usual options consist of preventive orthopaedic procedures such as curettage, internal fixation, and bone grafting.[14] These procedures were designed to control the extent of the lesion and to treat the pathologic fractures that often develop in the affected areas. Calcitonin, etidronate, and mithramycin as nonoperative therapy have been used in the past but with poor results.[2,9]

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However, recent developments in the use of second generation bisphosphonates have provided some viable choices for the treatment of patients with fibrous dysplasia. It is widely known that the pathology behind fibrous dysplasia lesions is an excess of osteoclastic activity with increased bone resorption. Excess osteoclastic activity also is attributed to other metabolic bone diseases such as Paget's disease and high turnover osteoporosis. Patients with these diseases have been treated successfully using the bisphosphonates. Two European groups reported earlier positive response to intravenous pamidronate therapy for fibrous dysplasia.[4,8]

The authors hypothesis is that oral bisphosphonates also could be used in the treatment of patients with fibrous dysplasia resulting in improved function, less pain, and prevention of pathologic fracture. The current study represents the initial experience of the first six patients with fibrous dysplasia treated with oral bisphosphonates with or without a loading dose of intravenous bisphosphonates with a minimum 2-year followup.

MATERIALS AND METHODS

Six patients with fibrous dysplasia (one male, five female) were followed up for a mean duration of 28 months. The mean age of the patients at the time of treatment was 45 years. The first four patients received 60 to 90 mg of pamidronate (Novartis, Inc, East Hanover, NJ) intravenously every 3 months for two doses and then received 10 mg alendronate (Merck, Inc, West Point, PA) taken orally every day. The patient with the highest N-Telopeptide received a dose of 40 to 80 mg every day. The last two remaining patients only received 10 mg of alendronate taken orally every day. The patients were evaluated after the initial consultation and after initiation of bisphosphonate therapy and at 6 months intervals thereafter. Pain analogue scores (0–10) were recorded at each visit to assess status of pain relief. Urinary N-telopeptide (collagen breakdown product) also was determined to evaluate bone turnover. Radiographs were obtained at each visit and assessed for new fractures and evidence of lesional resolution (diminution in size, ossification of lesion, evidence of cortical rim) by five reviewers blinded as to date. Before the initiation of bisphosphonate therapy, there was no significant improvement in disease status either radiographically or subjectively. None of these patients received any pharmacologic therapy for the treatment of their disease before the current study. All six patients had radiographic evidence of fibrous dysplasia, significant pain, and recent pathologic fractures before therapy (Figs 1,2,3).

Statistical analysis consisted of Wilcoxon signed ranks test for N-telopeptide values and pain analogue score. Statistical significance was achieved with $p < 0.05$.

RESULTS

Clinical Effects

All six patients in the study had significant clinical improvement. Before the first treatment, each patient complained of pain at the affected sites. On the pain analogue score of 0 to 10 with 10 being the most severe pain, the mean severity at baseline was 5 with a range from 1 to 8. The mean pain severity at 2 years followup was 1, with the pain analogue score recorded at 6, 12, 18, and 24 months. The average decrease at 2 years in pain score was 73% for those patients who only received alendronate and 75% decrease for those who received alendronate and pamidronate ($p < 0.03$) (Table 1).

Biochemical Changes

N-telopeptide values decreased significantly when the combination of pamidronate and oral alendronate was administered intravenously ($p < 0.05$) (Table 1). The N-telopeptide values remained essentially unchanged in the two patients who only received oral agents.

Radiographic Changes

No patient in the study had any new pathologic fractures develop during the followup period. One patient, who was doing extensive exercise on a treadmill, had a 4-mm lucent line develop on the tension side of the right femoral neck (Fig 2). This lucency disappeared within 2 months after her activity on the treadmill ceased. There also was an increase in the bone quality of the participants. Four of six patients in the study had early changes in their radiographs

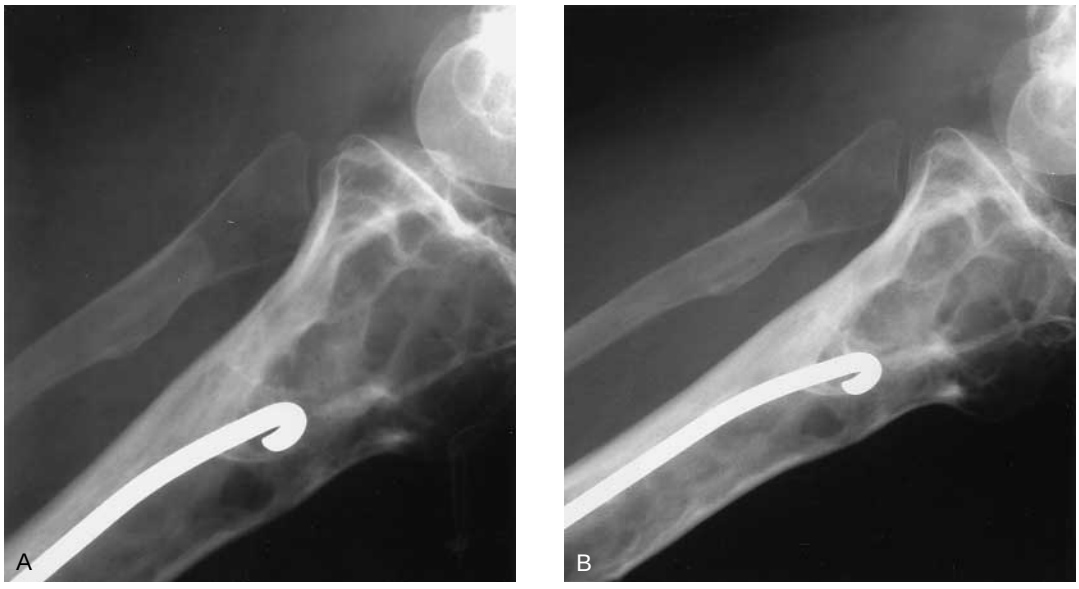

Fig 1A–B. Radiographs of a 47-year-old patient (Case 3) with polyostotic fibrous dysplasia obtained after treatment with intravenous pamidronate and oral alendronate. (A) Radiograph showing tibial lesions with a Rush rod from primary treatment. Within 2 years (B) the radiograph shows progressive ossification and clouding of lesion. Evidence of diminution of lytic lesion adjacent to the curve of the Rush rod is apparent.

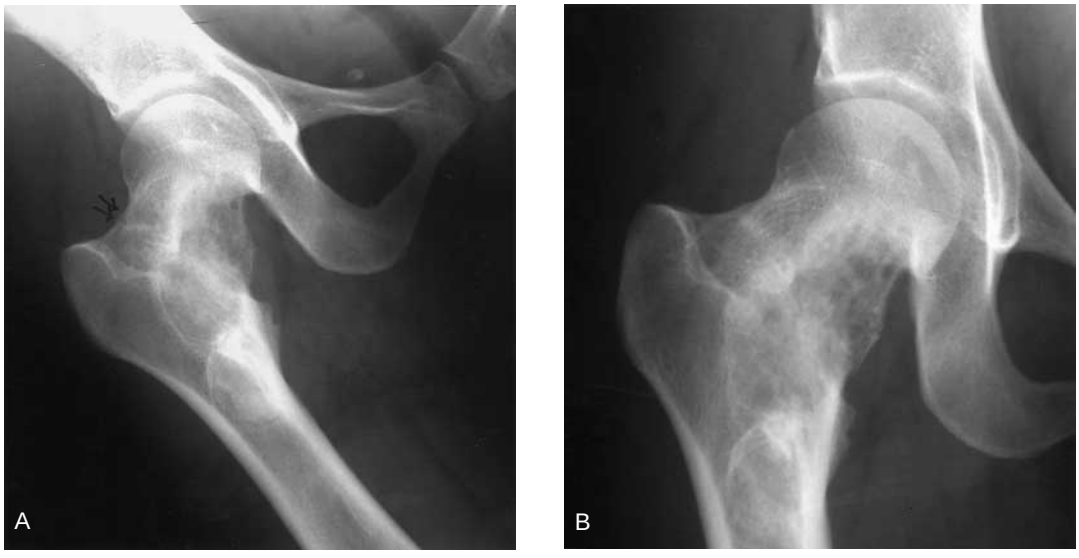

Fig 2A–B. (A) A 34-year-old woman (Case 5) taking oral alendronate alone for the treatment of fibrous dysplasia had a small stress line (arrows) develop on the tension side of the femoral neck after the use of a treadmill. (B) Within 6 months of bisphosphonate therapy, the patient had complete resolution of the stress line and enhanced ossification of the subtrochanteric lesion and trabecular filling of the calcar region.

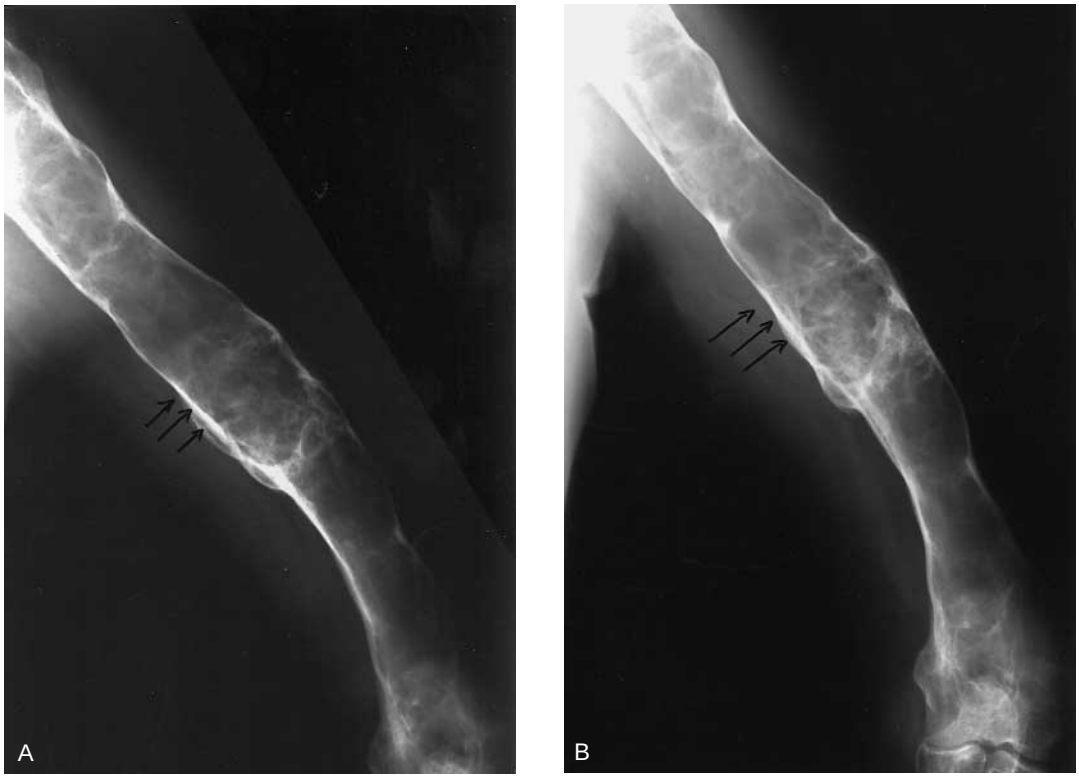

Fig 3A–B. A 57-year-old man (Case 4) with polyostotic fibrous dysplasia (McCune-Albright Syndrome) was treated with intravenous pamidronate and oral alendronate. (A) Radiograph of the patient's humerus showing extensive cystic disease within the cortex (arrows). (B) One year later there is evidence of partial trabecular ossification and significant cortical enhancement in the medial aspect of the middiaphysis (arrows).

TABLE 1. Effect of Bisphosphonate Treatment on Bone Turnover and Pain in Patients With Fibrous Dysplasia

Patient			N-telopeptide (Bone collagen breakdown product) Nmol BCE/mmol Cr		Pain Analogue Score	
Case	*Age (years)*	*Gender*	*Before Treatment*	*After Treatment*	*Before Treatment*	*After Treatment*
1	72	F	69	52	4	0
2	42	F	114	125	7	2
3	47	F	54	26	1	0
4	57	M	663	369	8	1
5	34	F	58	35	3	1
6	39	F	60	26	8	2
	Average		170	106#	5	1*

* = $p < 0.03$; # = $p < 0.05$; M = male; F = female.

consistent with cortical thickening (> 2 mm increase), progressive ossification of the lesion, and decrease in lesional diameter (> 20% decrease). Although these changes were subtle, they were present on each radiograph and this clearly represents improvement of the bone matrix and a lack of progression of the disease.

DISCUSSION

In the current study, a series of six patients with fibrous dysplasia treated with bisphosphonates is reported. All six patients did not have frank fractures and experienced improved function. Four of six patients had partial healing of the osseous lesions. All patients who received combination intravenous and oral therapy had a significant decrease in collagen breakdown products as compared with the patients who only received oral agents. Other than this difference in collagen biochemistry, there were no differences in the favorable response to either oral bisphosphonates alone or in combination with intravenous therapy regarding pain and fracture healing.

Liens et al[8] recognized that surrounding the advancing edge of fibrous dysplasia is a wave of activated resorbing osteoclasts. Assuming that resorption is a critical step toward expansion, Liens et al[8] and the current authors used a known family of drugs that inhibit osteoclast resorption. The mark of resorption is the breakdown of collagen and the release of nondegradable collagen fragments measurable either in the serum or urine. The N-telopeptide is a well documented measure of bone collagen resorption.[6] Active fibrous dysplasia is associated with high levels of the N-telopeptide (Table 1). The significant decline in values with bisphosphonates (inhibitors of osteoclasts) supports the concept of blocking expansion of the fibrous dysplasia and allowing a host healing response.

Of the six patients, four had the polyostotic type of fibrous dysplasia, and of these, two had McCune-Albright syndrome. The McCune-Albright syndrome is a sporadic disease characterized by polyostotic fibrous dysplasia, sexual precocity, cafe au lait spots, and increased function of various endocrine glands. G proteins are the source of the genetic defect in McCune-Albright syndrome and it is G protein that couple receptors for many hormones to effectors that regulate second messenger metabolism.[13] G protein dysfunction can involve gain or loss of function. Mutations in the Gs (alpha) gene that cause a loss of function are responsible for pseudohypoparathyroidism whereas gain of function mutations cause the McCune-Albright syndrome.[13] The mutation is found in fluctuating levels in the affected endocrine and nonendocrine areas, consistent with the mosaic pattern of abnormal cells generated by a somatic cell mutation early in embryogenesis.[12] The activating missense mutation of the alpha subunit of the Gs protein (Gs alpha) is found in the affected tissues. In addition, intracellular cyclic adenosine monophosphate content and interleukin-6 secretion by the cells were increased in those patients with mutations in the Gs (alpha) gene.[16] Yamamoto et al[16] indicated that the cells derived from the fibrous bone dysplasia tissues in patients with McCune-Albright syndrome produced increased levels of interleukin-6. Interleukin-6 synthesis has a pathogenic role in the bone lesions of patients with McCune-Albright syndrome and is responsible for the increased resorption in this disease via increasing the number of osteoclasts.[10]

An increased expression also has been reported of the protooncogene c-fos in patients with fibrous dysplasia, possibly attributable to the increase in intracellular adenylate cyclase.[3]

Liens et al[8] studied nine patients with symptomatic and severe fibrous dysplasia who were treated with intravenous pamidronate (60 mg per day for 3 days every sixth month) and were followed up for as many as 4 years. The major effect they observed was decreased bone pain. Thickening of cortices and refilling of osteolytic defects were seen in four of the nine patients. The initial increased bone remodeling was reduced as shown by decrease of raised serum alkaline phosphatase and urinary hy-

droxyproline. An additional followup of the original patient series was reported in a study by Chapurlat et al[4] who assessed the long-term effects of intravenous pamidronate in patients with fibrous dysplasia. In their study, 20 patients (11 males and nine females; mean age, 31 years) received courses of 180 mg of intravenous pamidronate every 6 months (60 mg/day during 3 days by infusion). The mean duration of followup was 39 months (range, 18–64 months). Severity of bone pain, number of painful skeletal sites per patient, radiographs of all involved areas, serum alkaline phosphatase, fasting urinary hydroxyproline, and urinary Type I collagen C-telopepide were assessed every 6 months. The severity of bone pain and the number of painful sites seemed to be reduced significantly. All biochemical markers of bone remodeling were lowered substantially. The authors reported a positive radiographic response in nine patients because they observed refilling of osteolytic lesions. Four of their patients sustained bone stress lines but no fracture occurred. They suggested that intravenous pamidronate alleviated bone pain, reduced the rate of bone turnover as assessed by biochemical markers and improved radiologic lesions of fibrous dysplasia.

A recent report by Pfeilschifter and Ziegler[11] reported the results of treatment of eight patients (three with fibrous dysplasia and five with McCune-Albright syndrome) with intravenous infusions of 60 mg of pamidronate. All patients had significant improvement of pain whereas two patients also had a reduction in size of some of the osteolytic lesions as seen on radiographs. They concluded that intravenous pamidronate was an effective and well-tolerated treatment option for patients with fibrous dysplasia.

The current series combined with the series by Chapurlat et al,[4] Liens et al,[8] and Pfeilschifter and Ziegler[11] strongly supports the use of bisphosphonates in the treatment of patients with symptomatic fibrous dysplasia. Unlike the patients in prior studies, the patients in the current study could be maintained on oral therapy after initial intravenous treatment. Those patients treated with oral agents alone appeared to do as well clinically as the patients who received combined therapy with the exception of no change in collagen breakdown products. Combination bisphosphonate therapy significantly diminishes pain, prevents fractures, and in the majority of patients, leads to partial resolution of fibrous dysplasia lesions within 2 years of therapeutic interventions. Second and third generation bisphosphonates already in use for diverse bone diseases (Table 2) seem to offer a successful medical strategy to combat the deforming disorder of fibrous dysplasia.

TABLE 2. Food and Drug Administration Approved Uses for Various Bisphosphonates

Bisphosphonate	Labeled Use
Alendronate	Glucocorticoid-induced osteoporosis
	Osteoporosis prevention
	Paget's disease
Pamidronate	Bone metastasis
	Hypercalcemia of malignancy
	Osteolytic bone metastasis
	Paget's disease
Etidronate	Heterotopic ossification
	Hypercalcemia of malignancy
	Malignant hypercalcemia
	Paget's disease
Risedronate	Paget's disease
	Primary hyperparathyroidism
Tiludronate	Paget's disease

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